REMARKS

The present claims concern double stranded compounds having a sense strand and an antisense strand and including at least one locked nucleic acid (LNA). The compounds are useful for siRNA mediated cleavage of mRNA.

Rejections under 35 USC §103

Claims 67-97 and 103 were rejected as obvious in view of Crooke (US 6,107,094) and Orum (US 2002/0068709). According to the Examiner, Crooke teaches single-stranded oligonucleotide that can bind to a target RNA, forming a substrate for double-stranded RNase (dsRNase). Also according to the Examiner, the oligonucleotides of Crooke can include a substituted nucleotide (e.g., a 2' methoxy nucleotide) that increases the binding affinity of the oligonucleotide for a complementary target RNA. The Examiner pointed out that Crooke, in Example 24 and Example 27-a, teach double-stranded compounds that act as artificial substrates for dsRNase. As the Examiner noted, Crooke does not suggest the use of LNA. The Examiner stated that Orum teaches the use of LNA in certain oligomeric compounds. The Examiner argued that it would have been obvious to one of ordinary skill in the art to "produce the artificial nuclease substrates of Crooke with one more LNA monomers as taught by Orum et al." The Examiner goes on to argue that the person of ordinary skill "would have reason to make modified substrates based on the teachings of Orum et al. that inclusion of LNA monomers provide nuclease resistance and extremely stable duplexes." The Examiner then goes on to assert that "the inclusion of multiple LNA moieties and the placement of the moieties to be a matter of design choice".

One would not be motivated to prepare an artificial double-stranded substrate containing LNA

Applicant disagrees with the Examiner's analysis. The double-stranded molecules of Crooke were used as artificial substrates to examine nuclease activity elicited by the single-stranded oligomers described by Crooke. As Crooke explains, the experiments using artificial substrates

in Example 24 were designed to examine the cellular distribution of deRNA activity elicited by the single stranded gapmer oligonucleotides. In Example 27-a, Crooke used artificial double-stranded substrates to develop and assay to develop an assay for the activity of dsRNase that did not suffer from interference due to the presence of single-stranded RNase in the cellular extracts.

In both Example 24 and Example27-a Crooke used the double-stranded molecules only as artificial substrates to test the single-stranded oligonucleotides containing 2'-methoxy nucleotides and phosophorothioate internucleotide linkages. The Examiner argues that because Orum teaches that LNA can stabilize double-stranded oligonucleotides, one would have been motivated to place LNA in the artificial substrates of Crooke. However, there would be no reason to put LNA into the artificial substrates since Crooke was only using them to explore the mechanism of cleavage by single-stranded oligonucleotides that contained 2'-methoxy nucleotides. The introduction of LNA into the substrates would not at all serve Crooke's purpose. Indeed, it would have interfered with Crooke's purpose. For this reason alone, the cited references, no matter how combined, cannot render the present claims obvious.

One would not turn to single-stranded anti-sense molecules to design double-stranded siRNA

Both Crooke and Orum concern single-stranded antisense compounds designed to elicit dsRNase activity when hybridized to a target mRNA. In contrast, the presently claimed molecules double-stranded compounds useful for eliciting cleavage of a target mRNA by an siRNA mechanism. As the Examiner is aware, the mechanism of dsRNase cleavage is completely different from siRNA mediated cleavage. Thus, one skilled in the art would <u>not</u> turn to the teachings of Crooke or Orum to design double-stranded siRNA molecules. For this second reason, the cited references, no matter how combined, cannot render the present claims obvious.

The examiner has not identified the rationale for the "design choice" that would make the claimed double-stranded compounds obvious

The Examiner did not individually address any of the dependent claims. Instead, apparently referring to all claims that specify the number and location of LNA in the compound, the Examiner asserted that "based on the broad disclosure of Crooke one of ordinary skill in the art would recognize the inclusion of multiple LNA moieties and the placement of these moieties to be a matter of design choice." The Examiner did not elaborate on the principles that would guide the design choice. Thus, it is difficult for the Applicant to address the Examiner's reason for concluding that the dependent claims are obvious. However, to the extent that Crooke provides a "broad disclosure" it is one directed to the design of single-stranded oligonucleotides that elicit dsRNase activity against a complementary mRNA and cannot be seen as providing any teaching directed to design choices for double-stranded oligonucleotides, much less double-stranded oligonucleotides useful for eliciting siRNA mediated mRNA cleavage. In addition, since, as the Examiner concedes, Crooke does not provide any teachings concerning LNA, one cannot see Crooke as providing any teaching directed to design choices for the use of LNA. Thus, the Examiner has failed to provide any *prima facie* case for concluding that any of the dependent claims are obvious.

In view of the forgoing, Applicant respectfully requests that the rejection of claims 67-97 and 102 under 35 U.S.C. §103 be reconsidered and withdrawn.

CONCLUSION

It is believed that the claims are in condition for allowance. The fee in the amount of $130.00 for Petition for One Month Extension Fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 22460-0041001.

Respectfully submitted,

Date: 5 July 2011

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